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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,556	07/26/2003	Jeffrey A. Ledbetter	30906/41458 CIP2	3297

4743 7590 12/08/2006

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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 12/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,556	LEDBETTER ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-79 and 81-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-79 and 81-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/04; 7/2/04; 3/21/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-79 and 81-109 are all the pending claims for this application.

2. Applicants have amended the claims in the Response of September 11, 2006 as follows:

Claim 1 recites an amino acid substitution "corresponding to amino acid position 11 of a heavy chain

variable region", and for which support can be found at [0091, 0121] of the specification; and

Claim 8 has been broadened from a single chain Fv to the single chain protein comprising amino acid substitutions at positions 9, 10, 12, 108, 110, 112 in the heavy chain variable region, and for which support can be found at [0091] of the specification. The amendments to the claims do not raises issues of new matter, accordingly the claims have been entered.

Examiner's Comments

3. The Examiner gratefully acknowledges the telephone conference of November 7, 2006 with Applicant's representatives, Mr. William K. Merkel and Ms. Kate Neville, to discuss the absence of sequence identifiers in the specification for the embodiments of the invention, more especially with respect to Claims 29, 30, 53 and 54, and the Examiner's inability to search any representative examples of the claimed embodiments. The Examiner understood that while Applicants agreed to assist in providing sequence identifiers for the aforementioned claims, in fact no deadline was

set for response. Thus in order to advance prosecution, the Examiner has examined all of the claims based on text searching alone.

Election/Restriction

4. Applicant's election with traverse of Group II (Claims 1-36, 37 in part, 38-58 and 61-75) in the reply filed on September 11, 2006 is acknowledged.
Applicants grounds for traversing the restriction of Groups 1-35 is that the Examiner has applied an inappropriate analysis of the claim restrictions pursuant to MPEP 802.01 (p. 14-17 of the Reply). Applicants assert that "to show distinctness, claimed subject matter must be shown to unconnected in design, operations and effect" and that "The Examiner has not addressed any design connection." Further Applicants assert pursuant to MPEP 806.05(j) that the Examiner has failed to satisfy criterion A and C in determining distinctness of the product inventions.

The Examiner has carefully reviewed Applicant's detailed statements in light of the protein molecules claimed in independent Claims 1, 76, 77 and 109 and more especially the narrowing amendment of Claim 1 to further limit the heavy chain variable region. The Examiner agrees to withdrawal of the restriction of the groups as it affects Claims 1-79 and 81-109.

5. The Examiner has considered the basis of Applicants grounds for traversing the species restrictions on pp. 17-24 of the Reply. First, with respect to all of the election of species requirements (reference to Sections 6-17 of the Office Action), Applicants reiterate that they "are not claiming" any of the speciated embodiments and that the

separate status given to any embodiment is irrelevant to the claimed product. It is well understood by the Examiner that none of the species is being claimed as a standalone invention. In further limiting the generic single chain protein or a specific scFv protein, a given species e.g., modifies the activity, introduces different chemical and structural properties, defines a target antigen for an scFv, etc., to affect or impart a structural or functional change to the generic single chain protein or a specific scFv protein. Applicants have not cited any binding precedent, which precludes the Examiner from speciating any one of the embodiments for its individual properties much less when the species is considered as a whole and in the context of the single-chain protein.

Nevertheless, in considering all of Applicants arguments traversing the speciation of the inventive groups under sections 6-17 of the Office Action, the Examiner has agreed to withdraw the species requirement. See the Examiner's rejection of the claims below.

6. Claims 1-79 and 81-109 are all the pending claims under examination.

Information Disclosure Statement

7. The U.S., international and foreign patent references and the non-patent literature references cited in the IDS' of July 2, 2004, December 22, 2004 and March 21, 2005 have been considered and entered with the following exception: reference BBBB on the 1449 form of July 2, 2004 does not include the journal name, volume, page number(s) or date of publication. Applicants are invited to furnish this information.

Otherwise, in the event the application was to be allowed, the reference would not appear on the face of the published patent.

Specification

8. The disclosure is objected to because of the following informalities:

a) The specification contains numerous places where the SEQ ID NOs are left blank, see for example, page 44. The claimed single-chain proteins cannot be cross-referenced to a corresponding or exemplary sequence in the Sequence Listing in the absence of sequence identifiers in the specification.

b) The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see for example p. 96, lines 7-8. Applicant is required to delete any embedded hyperlink(s) and/or other form of browser-executable code(s). See MPEP § 608.01.

The use of the trademarks, e.g., Panorex®, Antilfa®, Zevalin® (see p. 31 for example), has been noted in this application. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

c) The brief description of the drawings need to indicate Figure 6A and B, Figure 19A, B and C.

Claim Objections

9. Claims 57 and 59, and Claims 58 and 60 are objected to for reciting duplicate subject matter. Appropriate correction is required.

10. Claim 50 is objected to for omitting to insert a comma between "shiga toxin" and "Pseudomonas Exotoxin A".

11. Claims 53 and 54 are objected to for improper sequence compliance. The claims are required to recite a sequence identifier under 37 CFR 1.821(d) and MPEP 2422.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 3, 13-16, 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 3 recites the limitation "the one or more amino acid substitution or deletion in said heavy chain variable region". There is insufficient antecedent basis for this limitation in the claim, because Claim 1 recites "an amino acid substitution or deletion".

b) Claim 13 is indefinite for the recitation "des-leucine". The term is not defined in the specification and the Examiner's search of a commercial electronic database (PubMed- see attached copy) did not reveal any amino acid or analogue defining this term. Is this a typographical error?

c) Claims 14-16 are indefinite for reciting "an increased recombinant expression or stability" because in Claim 14 it is not clear how expression or stability can be recombinant. Do applicants mean that expression and stability of the recombinant protein of preceding Claim 12 is increased?

d) Claims 29 and 30 are indefinite for reciting that the single chain Fv is a "hd37 single chain fv, 2h7 single chain fv, g28-1 single chain fv, and 4.4.220 single chain fv" because it is not clear if the single chain protein or scFv is produced by the hybridoma as a single expressed protein, or whether the VH, VL, hinge region, heavy chain constant region or a combination of all of these domains are cloned from a hybridoma expressing the respective native antibody. The specification identifies several examples of single chain proteins where the various regions or domains are cloned from a hybridoma-expressing antibody, but does not disclose that single chain protein or scFv-Ig fusion protein is actually expressed by any one of the hybridomas.

The art teaches that a hybridoma is produced by the fusion between a B cell and a myeloma cell, which is a cancer cell that provides the resultant B cell-myeloma hybrid, or hybridoma, with the capacity to proliferate indefinitely (see Campbell et al, Biology, 5th ed. pg. 856, 1999). Thus, when read in light of the specification and in view of the knowledge in the art, one of ordinary skill in the art would not be reasonably apprised of the metes and bonds of "a scFv from" any one of the hybridomas as presently claimed because a hybridoma secretes or produces mouse antibodies of a single idiotype (i.e., the monoclonal antibodies produced from a given hybridoma are identical). Further, it is

unclear if the claims are directed towards the hybridoma or is some modified antibody that is genetically engineered such that other forms of monoclonal antibodies including single chain proteins or scFvs are produced by the hybridomas. It is unclear what is contemplated by the scFv embodiments and one of skill in the art could not determine the metes and bounds of the claimed invention as written. See the Examiner's further comments under section 13, infra.

e) Claim 30 is indefinite for reciting "FC2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36, G19-4, 1D8" for the reasons set forth supra. It is not clear how the scFv can be produced from the same hybridoma as the native antibody absent some modification to the hybridoma.

Biological Deposit Requirement

13. Applicants have submitted an extensive Sequence Listing of 699 individual sequences but have not provided the corresponding molecules in the specification with sequence identifiers for cross-referencing purposes. If the amino acid and/or nucleic acid sequence data for the claimed single chain proteins or scFv-Igs is provided in the sequence listing so that one of ordinary skill in the art could practice the claimed invention, i.e., making and using, then Applicants should not be required to meet the deposit requirement. However, the Examiner acknowledges that the single chain proteins and scFv-Igs are derived from hybridomas, and absent sufficient guidance in the specification for making the molecules and the public availability of the hybridoma cell lines, then the following deposit requirement applies to the HD37, G28-1, 4.4.220,

Fc2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36 and G19-4 hybridomas of claims 29, 30 and 83-108.

14. Claims 29, 30 and 83-108 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description.

a. It is unclear if a hybridoma cell line, which produces an antibody having the exact chemical identity of HD37, G28-1, 4.4.220, Fc2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36 or G19-4 is known and publicly available, or can be reproducibly isolated without undue experimentation. The Examiner's search of the ATCC website indicates that the 2H7 and 1D8 hybridomas are publicly available. The hybridomas HD37, G28-1, 4.4.220, Fc2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36 and G19-4 do not appear to have been deposited and would not be publicly accessible. See the attached copy of the Examiner's search output for the aforementioned hybridomas from the ATCC website. Applicants have not made any declarations in the specification that deposits have been made for these or any other hybridomas that would become available under the terms of the Budapest Treaty. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the

chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

b. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993); cited in the IDS of March 21, 2005]. Therefore, it would require undue experimentation to reproduce the claimed antibody species HD37, G28-1, 4.4.220, Fc2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36 or G19-4. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made

under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit

and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Scope of Enablement

15. Claims 1-79 and 81-109 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a) a binding domain-immunoglobulin fusion protein comprising a binding domain polypeptide which comprises an immunoglobulin light and heavy variable domain, and b) scFv-Ig fusion molecules with modified VH and VL regions cloned from a hybridoma and engineered to modify the amino acid positions, and c) scFv-Igs with amino acid substitutions at positions 9, 10, 11, 12, 108, 110 and 112 for the VH region comprising serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysinc, arginine, and histidine, does not reasonably provide enablement for a) a binding domain-immunoglobulin fusion protein comprising a binding domain polypeptide which

comprises only a light chain variable domain or only a heavy variable domain, b) a single chain antibody or scFv comprising any amino acid substitution or deletion in positions 9, 10, 11, 12, 108, 110 and 112 for the VH region and any amino acid substitution or deletion in one or more of positions 12, 80, 81, 83, 105, 106 and 107 for the VL region, and c) a modified VH (or VL) region or scFv-Ig comprising a modified VH (or VL) region produced from the hybridoma, 2H7, HD37, G28-1, 4.4.220, Fc2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36, 1D8 or G19-4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

a) The specification is not enabling for using single chain proteins having only a heavy chain domain (or only a light chain domain).

Claims 1, 3, 8, 25, 26, 33-52, 55-58, and 63-76 are broadly drawn to a binding domain polypeptide that has a heavy chain, which would not bind antigen because the molecule contains CDR1-3 from only one Ig chain. The specification does not enable a binding domain with only a heavy chain, but discloses single chain proteins and scFvs

with at least one heavy chain variable domain and at least one light chain variable domain.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979; cited in the IDS of March 21, 2005). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Thus, it is unlikely that scFv's as defined by the claims which may contain less than the full complement of CDRs from the heavy or light chain variable regions or comprise any amino acid substitution in the hypervariable region of the heavy chain or light chain variable domain, have the required binding function. The

specification provides no direction or guidance regarding how to produce single chain antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

b) The specification is not enabling for any single chain antibody or scFv comprising any amino acid substitution or deletion in positions 9, 10, 11, 12, 108, 110 and 112 for the VH region and any amino acid substitution or deletion in one or more of positions 12, 80, 81, 83, 105, 106 and 107 for the VL region.

Claims 1-9, 14-79, and 81-109 are drawn to single chain proteins and scFv-Igs comprising any amino acid substitution or deletion in positions 9, 10, 11, 12, 108, 110 and 112 for the VH region and/or any amino acid substitution or deletion in one or more of positions 12, 80, 81, 83, 105, 106 and 107 for the VL region.

The specification does not enable single-chain protein molecules that are modified in protein sequences at positions 9, 10, 11, 12, 108, 110, or 112 for the heavy variable domain or positions 12, 80, 81, 83, 105, 106 and 107 for the light chain with just any amino acid insertion, deletion, substitution, etc. The specification supports the following amino acid substitutions at positions 9, 10, 11, 12, 108, 110, or 112 of the VH region and especially for position 11: serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysinc, arginine, and histidine. The specification does not support the substitution of leucine at position 11 of the VH region with des-leucine.

The claims are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims, which encompass all modifications to the amino acid sequence because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonable correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f

Further protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin

binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

c) The specification is not enabling for making hybridomas which express scFv or scFv-Ig fusion proteins comprising VH (or VL) regions being modified at any amino acid position.

Claims 29, 30 and 83-108 are interpreted as scFv-Igs having position 9, 10, 11, 12, 108, 110 and 112-modified binding domains (VH) being produced from hybridomas 2H7, HD37, G28-1, 4.4.220, Fc2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36, 1D8 or G19-4.

Applicant has not shown that any of these hybridomas express an antibody comprising a VH domain possessing the claimed modifications for positions 9, 10, 11, 12, 108, 110 and 112 (or a VL domain modified at positions 12, 80, 81, 83, 105, 106 and 107). Applicants have cloned the VH and VL domains from an antibody expressed by the respective hyrbidoma and genetically engineered amino acid modifications into the claimed positions for the VH and VL domains, but the specification does not disclose the generation of any recombinant hybridomas that would express a molecule for or comprising the claimed modified VH (or VL) domain much less an entire scFv molecule. It is generally accepted in the art that scFv are produced by recombinant techniques from an idiotypic antibody expressed by a hybridoma (see Worn and Pluckthun (J. Mol. Biol. 305:989-1010 (2001) (describing strategies for producing recombinant scFVs with improved stability, especially Figure 4, listing CDR grafting, point mutation, etc. and methods for accomplishing these modifications using display libraries (see Figure 8)); Hollinger and Hudson (Nature Biotech. 23:1126-1136 (2005) (reporting preclinical and clinical studies for recombinant antibody fragments (Table 1) including engineering of IgGs into Fab, scFv an single variable VH and VL domains (p. 1127, Col. 1, ¶1).

The specification does not teach the method steps for producing the scFv-expressing recombinant hybridomas from the parent hybridoma cell lines. Thus one skilled in the art would be required to identify the appropriate constructs for transfecting cells if scFv encoded vectors were being used, selecting stable single-chain molecule expressing host cells under appropriate conditions, and screening supernantants for

scFvs with specific binding activity. Alternatively, if Applicants contemplate using the parent hybridoma cell lines to produce the modified VH or VL, then one skilled in the art would be required to site-specifically mutagenize nucleic acids encoding the amino acid of interest to obtain the modified VH or VL, and the specification is silent with respect to accomplishing this endpoint.

Conclusion

Therefore, in view of the lack of guidance and lack of predictability associated with regard to making and using the single chain proteins and scFv-Ig fusion proteins encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Priority

16. The later-filed application (i.e., the instant application) must be an application for a patent for an invention, which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See Transco Products, Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed Provisional application, 60/367,358 ('358) and non-provisional Application No. 10/053,530 ('530), fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or

more claims of this application. The '358 and '530 applications disclose scFv-Ig, scFv-ligand and scFv-Fc fusion proteins where the VH and VL regions for the scFv are cloned from the 2H7, HD37, L6 and G28-1 hybridomas. The '358 and '530 applications do not support modifications to VH or VL regions at any of amino acid positions 9, 10, 11, 12, 108, 110 and 112 of the heavy chain variable region and one or more amino acids at positions 12, 80, 81, 83, 105, 106 and 107 of the light chain variable region. Furthermore, the '358 and '530 applications do not contemplate making scFv proteins from any one of the Mabs, 4.4.220, Fc2-2, UCHL-1, 5B9, 10A8, 2e12, 40.2.36, G19-4 or 1D8.

Claims 1-79 and 81-109 are drawn to single-chain protein or a scFv-Ig fusion protein having an amino acid substitution or deletion at position 11 of the heavy chain variable region, the single-chain protein having further substitutions at positions 9, 10, 12, 108, 110 and 112 of the heavy chain variable region, and the scFv-Ig fusion protein having an amino acid substitution or deletion at position 11 of the heavy chain variable region and an amino acid substitution or deletion of one or more amino acids at positions 12, 80, 81, 83, 105, 106 and 107 of the light chain variable region. Therefore, the effective filing date of claims 1-79 and 81-109 for purposes of applying prior art is deemed to be the filing date of the 10/627,556 application, i.e., 7/26/2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 65, 68, 69, 71, 72, 76-79 and 109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shan et al (J.

Immunol. 162:6589-6595 (1999); hereinafter referred to as "Shan"; cited in the IDS of 7/2/04) in view of Pluckthun et al. (USPN 6,815,540; published 11/9/2004; filed 1/15/1999; hereinafter referred to as "Pluckthun").

Claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 65, 68, 69, 71, 72, 76-79 and 109 are drawn to a single chain protein comprising in the order of a scFv, a connecting region and a N-terminally truncated Ig heavy chain constant region, where the protein has an immunological activity, where the protein binds one target, where the VH of the scFv comprises an amino acid substitution or deletion at position 11, and one or more amino acid substitutions at positions 9, 10, 12, 108, 110, 112 of the VH region, where the amino acid substituted for position 11 is serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, and histidine, and dimers comprising two scFvs where the second scFv binds the same or a different target, where the replacement of leucine with serine at position 11 of the VH increases the stability and expression of the scFv-Ig from 10-100-fold, where the VL has an amino acid deletion or substitution at one or more of amino acid positions 12, 80, 81, 83, 105, 106, and 107, where the protein binds to cell-surface cancer antigens or antigens on immune effector cells, binds B-cell antigens such as CD20, where the protein forms a dimer or monomer, where the protein is coupled to a drug, toxin, immunomodulator, polypeptide effector, isotope, label, or effector moiety, where the protein has immunological activity such as ADCC, ACC, inducing apoptosis, biological signals, effector cells, cellular activation and differentiation, release of biological molecules, and neutralization of infectious agent or toxin and binding to an intracellular target, where

the linker comprises Gly-Gly-Gly-Gly-Ser or $(Gly\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Ser)_3$, variable domains are from mice, where the protein comprises a human IgG CH2 and CH3 regions, where cysteines are removed from the hinge in order to reduce dimerization, and where the hinge has a glycosylation site.

Shan teach a scFv that binds CD20 that has the linker Gly-Gly-Gly-Gly-Ser or $(Gly\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Ser)_3$, where the scFv is fused to a hinge that has the cysteines removed so it cannot dimerize and the hinge is fused to a CH2 and CH3 (human IgG1 Fc domain). Since the fusion protein has the hinge, CH2 and CH3, it is inherent that the protein has complement fixation or antibody-dependent cell-mediated cytotoxic properties, which further involve biological signaling, effector cell function, cellular activation and differentiation, release of biological molecules, and would also result in neutralization of infectious agent or toxins. Shan discloses the scFv-Ig molecule having apoptosis-inducing activity for a CD20-expressing tumor cell line. Since the molecule induces apoptosis, it is inherent that the protein induces activation of cellular signals, and up- and down-regulation of transcription. Shan teaches that the scFv-Ig constructs are useful for targeted immunotherapy of CD20-expressing B-cell malignancies including applications involving radionucleide conjugates and pretargeting strategies using scFv-streptavidin conjugates in combination with biotin-^{90}Y secondary reagents. Since the molecule has other targeting properties, it is inherent that the protein can bind to an intracellular target to affect a function. Shan does not teach introducing amino acid substitutions into the VH or VL regions of the scFv, that residues 9, 10, 11, 108, 110 and 112 of the HV and residues 12, 80, 81, 83, 105, 106 and 107 of the VL are

substitutable, that the modifications confer increased production vis-à-vis increased stability, and that the modified scFvs can be fused to toxins, bacterial or viral-derived molecules or cytokines for further bio-affecting properties. Pluckthun rectifies these deficiencies in its disclosure.

Pluckthun discloses introducing into the VH and VL regions, combinations of amino acid substitutions, insertions and deletions effected to reduce the hydrophobicity, or which otherwise increase the solubility and levels of expression for the antibody molecules and fragments. Pluckthun discloses the amino acid(s) which replace(s) the more hydrophobic amino acids include Asn, Asp, Arg, Gln, Glu, Gly, His, Lys, Ser, and Thr. Pluckthun discloses that residues 9, 10, 12, 15, 39, 40, 41, 80, 81, 83, 103, 105, 106, 106A, 107, 108 for VL, and residues 9, 10, 11, 13, 14, 41, 42, 43, 84, 87, 69, 105, 108, 110, 112, 113 for VH, are preferred positions for modifications. Pluckthun discloses VH- and VL-modified antibody molecules and fragments being linked by the $(Gly4Ser)_3$ peptide and further fused to other moieties which have a useful therapeutic function such as bacterial toxins Pseudomonas exotoxin A, and diphtheria toxin, virus surface molecules, plant toxins ricin, abrin, modeccin, saporin, and gelonin, and a cytokine, such as IL-2. Pluckthun discloses an example of a scFv mutant at VH position 11 (Flu6 (L11D/V84D) (FIG. 3B lane 7, 8) that yielded about 0.25 mg per liter of protein whereas the wt scFv antibody did not give any soluble protein. Because the molecules comprise other effector molecules, it is inherent that protein as a whole has cell signaling properties, viral, bacterial and toxin neutralizing properties, and immune cell inducing properties.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have created a scFv-Ig fusion molecule against CD20 as taught by Shan and to have modified the molecule according to Pluckthun which teaches introducing amino acid substitutions or deletions in the VH and VL of antibody fragments in order to obtain more stable and increased production of the molecules.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have determined the molecule of the instant claims based on the disclosure of Shan and Pluckthun. One skilled in the art would have been motivated to have modified the molecule of Shan who teaches in general that the scFv-Ig constructs are useful for targeted immunotherapy of malignancies including applications involving secondary reagents, and importantly, that the constructs are amenable to further structural modifications (p. 6954, Col. 2). One skilled in the art would have been motivated to have introduced protein stabilizing and protein-expression enhancing modifications into VH and VL regions of the scFv-Ig of Shan based on the teachings of Pluckthun, because Pluckthun teaches that antibody fragments can be obtained in improved yields compared to wild-type molecules with the introduction of position-critical amino acid substitutions or deletions that specifically affect protein yield.

One skilled in the art would have had a reasonable expectation of success in producing the instant claimed scFv-Igs based on the combined disclosures because the Pluckthun discloses which positions are critical and what amino acids can be

substituted (or deleted) for these positions for scFvs, per se, and because the binding domains according to Shan are scFv comprising VH and VL domains. One skilled in the art would have had a reasonable expectation of success in producing the instant claimed scFv-Igs based on the combined disclosures of Shan and Pluckthun because Pluckthun discloses that increased stability and protein yields are not compromised when scFvs are fused to other bio-affecting molecules. Thus further modifications of the scFv as taught by Shan, e.g., Ig fusion or bio-affecting proteins, would not have compromised the intended effect of introducing amino acid modifications into the VH and VL for increasing yield.

Thus the instant claimed invention was prima facie obvious at the time the invention was made, based on the combined reference disclosures.

18. Claims 1, 56, 65 and 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shan in view of Pluckthun as applied to claim 1 above, and further in view of Bodmer et al. (USPN 5,677,425; published 10/14/1997; hereinafter referred to as "Bodmer"; cited in the IDS of 12/22/04).

The interpretation of Claim 1 is discussed supra. Claim 56 is drawn to a humanized variable region and Claims 65 and 70-72 are drawn to modified hinge regions having only one cysteine with reduced dimerization.

The interpretation of Shan and Pluckthun is described supra. Shan also teaches making antibodies smaller while retaining bivalent binding properties (p. 6594). Shan

and Pluckthun do not teach a mutated hinge region containing one cysteine. Bodmer rectifies this deficiency.

Bodmer discloses an antibody where the hinge is modified to have one cysteine and the variable regions and the constant regions can be humanized (Col. 1, lines 25-33; Col. 3, lines 14-67). Since the hinge has only one cysteine, it would be inherent that it would have a reduced ability to dimerized and since the fusion protein has the hinge, CH2 and CH3 domains, it is inherent that the protein would have biological properties. Bodmer discloses that mutations to reduce the cysteines in the hinge have the advantage that it will facilitate assembly of the antibody molecules (Col. 3, lines 60-63).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the claimed invention was made to have used the hinge region of Bodmer in the construct of Shan in view of Pluckthun.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Bodmer in the construct of Shan because Shan teach that they are focusing on making antibodies that are bivalent. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Bodmer in the scFv-Ig construct of Shan in view of Pluckthun because Bodmer teach reducing the cysteine residues in the hinge to one residue facilitates the assembly of antibody molecules. Thus, it would have been obvious to one of ordinary skill in the art to have used the hinge region of Bodmer, which has a single cysteine residue, and substitute

this hinge for the hinge in Shan in order to produce an antibody which had the affinity of an intact antibody because it would have two binding sites.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

19. Claims 1, 63, 66 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shan in view of Pluckthun as applied to claims 1 and 77 above, and further in view of Bodmer and Morrison et al. (USPN 6,284,536; published 9/4/2001; filed 8/11/98; hereinafter referred to as "Morrison"; cited in the IDS of 3/21/05).

The interpretation of Claims 1 and 77 is discussed supra. Claims 63, 66 and 82 are drawn to wild type or modified IgA hinge containing one cysteine.

The interpretation of Shan and Pluckthun is described supra. Shan also teaches making antibodies smaller while retaining bivalent binding properties (p. 6594). Shan and Pluckthun do not teach a mutated hinge region containing one cysteine or an IgA hinge or mutated IgA hinge or a variable region from a human immunoglobulin. Bodmer and Morrison rectify these deficiencies.

The interpretation of Bodmer is discussed supra. Bodmer discloses mutations to reduce the cysteines in the hinge have the advantage that it will facilitate assembly of the antibody molecules (Col. 3, lines 60-63).

Morrison discloses an antibody having an IgA hinge.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the hinge region of Morrison or

mutate the hinge regions as taught by Bodmer used in the scFv-Ig fusion construct of Shan in view of Pluckthun.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Morrison or mutate the hinge regions as taught by Bodmer in the construct of Shan in view of Pluckthun because Shan teaches making antibodies that are bivalent. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Morrison or mutate the hinge regions as taught Bodmer in the construct of Shan in view of Pluckthun because Bodmer teach reducing the cysteine residues in the hinge to one residue facilitates assembly of antibody molecules. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Morrison et al or mutate the hinge regions as taught by Bodmer in the construct of Shan in view of Pluckthun because Morrison teach the benefits of an IgA Fc and specifically an IgA with a hinge region. Thus, it would have been obvious to one of ordinary skill in the art to have used the hinge region of Morrison or mutate the IgA hinge region as taught by Bodmer which has a single cysteine residue and substitute this hinge for the hinge in Shan in order to produce an antibody which had the affinity of an intact antibody because it would have two binding sites.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

20. Claims 1, 64, 67 and 73-75, 77 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shan in view of Pluckthun as applied to claims 1 and 77 above, and further in view of Roux et al. (J. Immunol. 161:4083-4090 (1998); hereinafter referred to as "Roux").

The interpretation of Claim 1 and 77 are discussed supra. Claims 64, 67, 73-75, and 81 are drawn to IgE hinges, wild-type IgG1 hinges and praline and cysteine substituted hinges, and hinges having amino acids in the following N-terminal order: Cys, Cys, Cys, Pro.

The interpretation of Shan and Pluckthun is described supra. Shan and Pluckthun do not teach IgE hinges, wild-type IgG1 hinges and praline and cysteine substituted hinges, and hinges having amino acids in the following N-terminal order: Cys, Cys, Cys, Pro . Roux rectifies these deficiencies.

Roux discloses hinge fold flexibility function for wild-type hinges for IgE and IgG1 and Cys- and Pro-modified hinges (Table 1 and Table 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the hinge regions of Roux or mutate the hinge regions as taught by Roux used in the scFv-Ig fusion construct of Shan in view of Pluckthun.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Roux or mutate the hinge regions as taught by Roux in the construct of Shan in view of Pluckthun because Shan teaches making small antibodies Shan also teaches making antibodies smaller

while retaining bivalent binding properties. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Roux or mutate the hinge regions as taught Roux in the construct of Shan in view of Pluckthun because Roux teaches modifying the cysteine and praline residues in the hinge facilitates antibody folding. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Roux or mutate the hinge regions as taught by Roux in the construct of Shan in view of Pluckthun because Roux teach the benefits of these hinge regions in modifying antibody folding. Thus, it would have been obvious to one of ordinary skill in the art to have used the hinge region of Roux or mutate the hinge region as taught by Roux and substitute these hinge regions for the hinge in Shan in order to produce an antibody which had the affinity of an intact antibody because it would have two binding sites.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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